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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,625	08/24/2006	Antonello Pietrangelo	LABM-11	2297

7590
Clifford W Browning
Krieg DeVault
One Indiana Square
Suite 2800
Indianapolis, IN 46204

01/22/2009

EXAMINER

MAIER, LEIGH C

ART UNIT	PAPER NUMBER
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1623

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/590,625	Applicant(s) PIETRANGELO ET AL.	
	Examiner Leigh C. Maier	Art Unit 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-36 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-36 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____. |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>8/24/06</u> . | 6) <input type="checkbox"/> Other: ____. |

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DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 33-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 33-36 provide for the use of hyaluronic acid esterified with rhein, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 33-36 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

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such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-6 and 22-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamura et al (EP 1082963) and Smith et al (Arthritis & Rheum., 1999).

Tamura teaches the preparation of a conjugate of a therapeutic agent for joint diseases, such as arthritis, and hyaluronic acid (HA) or a salt thereof. The agent may be attached to HA at a hydroxyl group by activating a carboxyl group in the therapeutic agent to prepare an ester linkage. See abstract and paragraphs [0001]; [0057]-[0059]; and [0072]-[0077]. The reference further teaches the preparation of a pharmaceutical composition of the conjugate. The pharmaceutical composition may be prepared in a form suitable for local or parenteral

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administration. See paragraph [0086]. The reference is silent regarding the concentration and pH of said composition. The reference teaches the general use of these therapeutic agents, see paragraph [0034], but is silent regarding rhein or a derivative thereof.

Smith teaches that diacerhein (diacetylated rhein) has utility for the treatment of osteoarthritis. See abstract.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the product of Tamura by the use of rhein, or a derivative, such as diacerhein, as the therapeutic agent to be conjugated to HA for the treatment of osteoarthritis with a reasonable expectation of success because this agent is known to be useful for this therapeutic method. In the absence of unexpected results, it would be within the scope of the artisan to optimize the level of esterification of HA in preparing the conjugate through routine experimentation. It would be further within the scope of the artisan to optimize the concentration of the conjugate in a composition, as well as the pH of the composition for this utility through routine experimentation. With respect to the claims to medical “products” and “devices” the examiner finds no requirements for these products not provided by a pharmaceutical composition, per se.

Claims 1-11 and 22-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamura et al (EP 1082963) and Smith et al (Arthritis & Rheum., 1999) in view of Nguyen (US 5,612,321).

Tamura teaches as set forth above. The reference further teaches the purification of conjugates by various methods, including dialysis. See paragraph [0084].

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Smith teaches as set forth above.

The references do not teach the preparation of a conjugate comprising reacting the acid chloride of rhein, or derivative or the preparation of said acid chloride.

Nguyen teaches also the preparation of HA-drug conjugates for the treatment of various disorders, such as osteoarthritis. These conjugates are more limited in scope, wherein the therapeutic agent is an antioxidant. See col 4, lines 1-49 and col 7, lines 55-67. The reference further teaches the preparation of an acid chloride of the therapeutic agent (treatment of precursor carboxylic acid with an excess of thionyl chloride in nonpolar aprotic solvent) to be conjugated as well as its reaction with HA. See examples 1 and 6.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to use any known synthetic organic technique, such as an acid chloride reactant for the esterification of HA, to prepare a conjugate of rhein, or derivative thereof. It would be within the scope of the artisan to optimize the relative amounts of the reactants in order to obtain an appropriately modified HA for the utility set forth by Tamura through routine experimentation.

Claims 1-15 and 22-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamura et al (EP 1082963) and Smith et al (Arthritis & Rheum., 1999) in view of Nguyen (US 5,612,321) and Hubbell et al (US 5,834,274).

Tamura and Smith teach as set forth above.

Nguyen teaches as set forth above. The reference does not teach the preparation of the HA conjugate in nonpolar aprotic solvent in the presence of a hydrogen ion acceptor, such as

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triethylamine. However, the use of these conditions for the acylation of a compound using an acid chloride is known in the art. See, for example, Hubbell at examples 1 and 2.

It would be obvious to one having ordinary skill in the art at the time the invention was made to prepare a rhein-HA conjugate, as discussed above. It would be further obvious to select any appropriate reaction conditions, such as those disclosed by Hubbell, for the reaction of the acid chloride reactant with HA with a reasonable expectation of success. With respect to the use of cyclohexane as a solvent for the acylation, it is noted that, given the use of benzene, it would be within the scope of the artisan to select another similar nonpolar, hydrocarbon solvent, such as cyclohexane (hydrogenated benzene) for this reaction. There does not appear to be any criticality in the use of cyclohexane. It would be further obvious to optimize the reaction time through routine experimentation based on the amount of esterification desired—that is, the amount of the therapeutic agent to be incorporated.

Claims 1-11 and 16-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamura et al (EP 1082963) and Smith et al (Arthritis & Rheum., 1999) in view of Nguyen (US 5,612,321) and Kuhla et al (US 4,788,187).

Tamura and Smith teach as set forth above.

Nguyen teaches as set forth above. The reference does not teach the preparation of said acid chloride using methylene chloride as the solvent or an inert atmosphere for the reaction. However, these are typical reaction conditions known in the art. See, for example, Kuhla at example 2 (step 1) at col 20.

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It would have been obvious to one having ordinary skill in the art at the time the invention was made to use any known synthetic organic technique, such as an acid chloride reactant for the esterification of HA, to prepare a conjugate of rhein, or derivative thereof, as set forth above with a reasonable expectation of success. In the absence of unexpected results, it would be within the scope of the artisan to select appropriate reaction conditions for the preparation of the acid chloride, based on those known in the art. It would be further within the scope of the artisan to select any known method, such as dialysis, as suggested by Tamura, for the purification of the HA conjugate.

Examiner's hours, phone & fax numbers

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leigh Maier whose telephone number is (571) 272-0656. The examiner can normally be reached on Tuesday, Thursday, and Friday 7:30 to 4:00 (ET).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Anna Jiang (571) 272-0627, may be contacted. The fax number for Group 1600, Art Unit 1623 is (571) 273-8300.

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/Leigh C. Maier/
Primary Examiner, Art Unit 1623
January 15, 2009